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ORIGINAL ARTICLE

Executive function subdomains are associated with post-stroke functional outcome and permanent institutionalization

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Background and purpose: Impairment of executive functions (EFs) is a common cognitive symptom post-stroke and affects independence in daily activities. Previous studies have often relied on brief cognitive tests not fully considering the wide spectrum of EF subdomains. A detailed assessment of EFs was used to examine which of the subdomains and tests have the strongest predictive value on post-stroke functional outcome and institutionalization in long-term follow-up.

Methods: A subsample of 62 patients from the Helsinki Stroke Aging Memory Study was evaluated with a battery of seven neuropsychological EF tests 3 months post-stroke and compared to 39 healthy control subjects. Functional impairment was evaluated with the modified Rankin Scale (mRS) and Instrumental Activities of Daily Living (IADL) scale at 3 months, and with the mRS at 15 months post-stroke. Institutionalization was reviewed from the national registers of permanent hospital admissions in up to 21-year follow-up.

Results: The stroke group performed more poorly than the control group in multiple EF tests. Tests of inhibition, set shifting, initiation, strategy formation and processing speed were associated with the mRS and IADL scale in stroke patients. EF subdomain scores of inhibition, set shifting and processing speed were associated with functional outcome. In addition, inhibition was associated with the risk for earlier institutionalization.

Conclusions: Executive function was strongly associated with post-stroke functional impairment. In follow-up, poor inhibition was related to earlier permanent institutionalization. The results suggest the prognostic value of EF subdomains after stroke.

Introduction

Post-stroke cognitive impairment is very common after stroke, even in patients with successful clinical recovery [1]. In particular, executive functions (EFs) are frequently impaired [1,2]. In a stroke cohort study, the prevalence of EF impairment was 49% amongst all stroke patients and 34% amongst patients with excellent clinical recovery [1].

Executive functions refer to higher cognitive control functions consisting of several subcomponents such as task setting, initiation, monitoring one's behaviour and self-regulating functions [3,4]. Executive processes are primarily mediated by prefrontal cortical regions and frontal-subcortical circuits [5,6]. These brain regions are susceptible to the effects of aging [7], and therefore differentiating stroke-related deficits from normal aging can be challenging.

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Impairments in EFs have been associated with post-stroke disability in basic [8,9] and instrumental [9] activities of daily living, and even with post-stroke mortality [10,11]. In previous studies, constricted test batteries have often been used to evaluate overall executive performance, and the significance of more specific executive processes and subdomains for functional outcome has remained unclear.

Traditionally, the Trail Making Test has been used in clinical neuropsychological assessment for evaluation of flexible action shifting, the Wisconsin Card Sorting Test (WCST) for set shifting, maintenance and abstraction, the Stroop test for inhibition, and the verbal fluency test for productivity and initiation [12]. However, successful test performance requires several different cognitive abilities apart from EFs (e.g. attention, working memory, language skills and perception), and individuals can fail in a particular test for many reasons [4]. There is still no gold standard for measuring EFs [13], and more sensitive methods are needed to detect the deficits associated with functional impairments. The Hayling sentence completion test [14], the questioning task [15] and the design fluency task [16] are less often used tests of EFs, and their usefulness in the stroke population is not well known.

In this study, the significance of different EF subdomains for functional outcome was investigated by using a comprehensive battery of traditional and unconventional neuropsychological EF tests in older patients with ischaemic stroke. The aims of the study were (i) to clarify which EF tests are able to identify stroke-related executive impairments, (ii) to explore the association of EF subdomains and test performance with functional abilities 3 and 15 months post-stroke and (iii) to examine the predictive value of EF subdomain impairments on patients' future need for permanent institutional care in long-term follow-up.

Methods

Subjects and study protocol

The subjects were a subgroup (n = 62) from the Helsinki Stroke Aging Memory Study (SAM). The original SAM cohort included 486 ischaemic stroke patients, aged 55–85 years, consecutively admitted to the emergency room of Helsinki University Hospital [17]. Three months after the index stroke, the patients went through clinical examinations and brain magnetic resonance imaging. Stroke severity was assessed with the National Institutes of Health Stroke Scale (NIHSS) [18]. Functional abilities were evaluated with the modified Rankin Scale (mRS) [19] and the Lawton Instrumental Activities of Daily Living (IADL) scale [20]. A comprehensive neuropsychological examination was completed by 409 patients [1]. For the present study, 107 subjects were taken consecutively from the original sample for more detailed examination of EFs. After exclusions [not completing the entire initial neuropsychological examination (n = 13), refusal (n = 13), lack of cooperation (n = 2) and other reasons (n = 17)], a subsample of 62 stroke patients underwent a subsequent neuropsychological examination focusing on EFs in more detail.

The same neuropsychological examinations were also carried out for 39 neurologically healthy age-, sex- and education-matched control subjects derived from an earlier population-based study [21]. The study protocol was approved by the Ethics Committee of the Department of Neurology, Helsinki University Hospital, Finland. Subjects gave written informed consent before participating in this study.

Fifty-eight stroke patients of this subsample were reached for follow-up 15 months after stroke. mRS was repeated either at a follow-up visit (n = 44) or by phone (n = 14). In the 21-year follow-up, information concerning permanent institutionalization was reviewed for all patients from national registers kept by the National Institute for Health and Welfare and the City of Helsinki, Bureau of Social Welfare. A patient was considered as permanently institutionalized when residing for more than 2 months in a nursing home or hospital at the end of the follow-up or at the time of death.

Neuropsychological assessments

The neuropsychological examinations were carried out in two separate sessions approximately 3 months after the stroke. The first neuropsychological evaluation covered multiple cognitive domains such as memory functions, attention, language and visuoperceptual abilities, and abstract reasoning as described before [1]. Within a few weeks, the patients came to another visit to complete a detailed examination focusing on EFs. In all, EFs were studied with seven tests: the Trail Making Test, the Stroop test, the modified WCST, verbal fluency, the Hayling sentence completion test, design fluency and the questioning task. With the Trail Making Test, the total time to complete the test was divided by the number of correct responses (time/score) in both parts separately to rule out the effects of different tactics (slow with correct answers or fast with many errors) on outcome [22]. The tests are described in detail in Table S1. The test variables are presented in Table 1.

Table 1 Evaluated executive function subdomains

Executive subdomain	Neuropsychological test	Variables
Processing speed	Trail Making A	Time/correct response
	Stroop A	Time to complete the test
	Hayling A	Sum of response latencies
Response inhibition	Stroop B	Error score, time to complete the test
	Hayling B	Error score, sum of response latencies
Set shifting	Trail Making B	Time/correct responses
	WCST	Number of correct responses
Initiation	Verbal fluency	Number of correct responses
	Design fluency	Number of correct responses
Strategy formation	WCST	Number of correct categories
	Questioning task	Number of constraint seeking questions

WCST, Wisconsin Card Sorting Test.

Statistical analyses

Patients and control subjects were compared to each other with the independent samples *t* test and with the non-parametric chi-squared test or Mann–Whitney *U*, where appropriate. Because of multiple comparisons, a more conservative *P* value of 0.01 was used.

Five composite scores of stroke patients for the EF subdomains were constructed from *z*-standardized test scores normalized according to the control group by calculating the mean scores of tests within the same subdomain (Table 1). This grouping was based on theoretical assumptions instead of statistical factor modelling [12]. In stroke patients, the associations of EF subdomains and tests with mRS and IADL were analysed with logistic regression models in two steps: model 1 was adjusted for age, sex and years of education, and model 2 was additionally adjusted for NIHSS. Functional impairment was defined as mRS score >2 and IADL score <7. The association between EF subdomains and permanent institutionalization was studied with Cox regression survival analyses adjusted for demographic variables and stroke severity.

The proportion of missing values in individual EF tests ranged from 0% to 15.8%. Missing values in the Trail Making Test were associated with a higher NIHSS score ($\chi^2 = 56.55$, $P < 0.001$), but there were no other significant associations between missing data and the demographic or clinical background variables.

Results

Compared with the original SAM cohort ($n = 485$), the patients of this subsample had milder stroke symptoms 3 months post-stroke (NIHSS score 1.94 vs. 3.58; $P = 0.001$), were younger (68.4 vs. 71.6 years; $P = 0.027$) and had less education (7.8 vs. 9.2 years in total; $P = 0.012$) but did not differ in stroke history ($\chi^2 = 1.79$; $P = 0.617$) or in Mini-Mental State Examination (MMSE) score (25.8 vs. 25.0; $P = 0.192$). The characteristics of the patients and controls are summarized in Table 2. No significant differences were observed between the stroke and control groups in demographic variables, but the control subjects received higher scores on MMSE than the stroke patients (Table 2). None of the subjects met the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), criteria for dementia at baseline.

Comparisons between the groups in individual EF test scores are presented in Table 3. Performance in

Table 2 Characteristics of the patients and controls

	Stroke	Control	*P*
Age, years, mean (SD)	68.4 (7.7)	67.4 (5.3)	0.490
Education, years, mean (SD)	7.8 (4.7)	9.4 (3.5)	0.084
MMSE, mean (SD)	25.8 (3.6)	28.2 (2.0)	<0.001
Sex (men), *n* (%)	32 (51.6)	18 (46.2)	0.593
NIHSS, *n* (%)			
0	27 (43.5)		
1–4	26 (41.9)		
5–15	8 (12.9)		
16–20	1 (1.6)		
21–42	0 (0)		
Previous clinical stroke, *n* (%)			
0	49 (79.0)		
1	13 (21.0)		
Total number of infarcts on MRI[a], *n* (%)			
0–1	22 (35.5)		
2–3	24 (38.7)		
≥4	16 (25.8)		
Left, *n* (%)			
0–1	42 (67.8)		
2–3	19 (30.7)		
≥4	1 (1.6)		
Right, *n* (%)			
0–1	37 (59.7)		
2–3	23 (37.1)		
≥4	2 (3.2)		
White matter hyperintensities (Fazekas scale), *n* (%)			
None to mild	22 (35.5)		
Moderate	13 (21.0)		
Severe	27 (43.5)		

MMSE, Mini-Mental Status Examination; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale. [a]Including all infarcts and lacunes whether or not related to clinical symptoms.

Table 3 Executive function test performance in stroke patients and control subjects

	Stroke, mean (SD)	Control, mean (SD)	*t*/*U*	*P*
Hayling A, time	49.84 (33.28)	39.46 (26.45)	1.65	0.103
Hayling B, time	115.57 (74.61)	77.95 (45.29)	−3.14	0.002
Hayling B, error score	10.82 (9.27)	3.49 (3.32)	549.00[a]	<0.001
Trail Making A (time/correct)	4.20 (5.08)	2.63 (1.17)	2.30	0.024
Trail Making B (time/correct)	17.96 (24.60)	7.90 (4.51)	2.84	0.010
Stroop A, time	22.03 (11.97)	18.42 (4.91)	1.77	0.038
Stroop B, time	46.79 (17.37)	37.43 (17.85)	−2.83	0.006
Stroop B, error score	3.07 (5.61)	0.16 (0.44)	713.00[a]	<0.001
WCST, number of correct responses	20.11 (11.15)	27.79 (10.72)	651.00[a]	0.001
WCST, number of correct categories	3.05 (1.88)	4.5 (1.81)	660.00[a]	<0.001
Verbal fluency, semantic	17.24 (6.69)	20.58 (4.62)	−2.95	0.004
Verbal fluency, phonetic	11.13 (5.76)	14.92 (4.35)	−3.47	0.001
Design fluency	4.51 (2.17)	5.37 (2.83)	915.00[a]	0.065
Questioning task, CS	2.35 (2.34)	3.42 (2.23)	836.00[a]	0.001
Questioning task, PC	0.67 (1.25)	1.21 (1.66)	918.00[a]	0.026
Questioning task, HT	2.05 (2.45)	1.18 (1.98)	921.00[a]	0.041
Perseverative errors, total	10.24 (6.80)	5.34 (5.84)	921.00[a]	<0.001

CS, constraint seeking questions; HT, hypothesis testing questions; PC, pseudo constraint questions; WCST, Wisconsin Card Sorting Test. (See Table S1 for a detailed description of neuropsychological test variables.) Independent sample *t* test; [a]Mann–Whitney *U*.

nearly all the EF tests differed between the stroke and control groups (Table 3). However, according to the more stringent criteria of significance ($P < 0.01$), differences in Hayling B and Stroop B, Trail Making B, WCST, verbal fluency and the questioning task remained significant. Moreover, stroke patients made significantly more perseverative errors in EF tests in total compared to the control group.

The relationships between EF subdomains and functional impairment defined as mRS >2 and IADL <7 at 3 months and mRS >2 at 15 months post-stroke are presented in Table 4. All five EF subdomains were significantly associated with mRS 3 months after stroke as analysed with logistic regression analyses adjusted for age, sex and education ($P < 0.05$). After additionally adjusting for stroke severity (NIHSS score), inhibition, processing speed and initiation remained significant. IADL 3 months post-stroke was predicted by inhibition, processing speed and set shifting. When NIHSS was added in the model, inhibition remained as a significant predictor. mRS 15 months post-stroke was predicted by set shifting regardless of stroke severity. Associations of the individual EF test scores with mRS and IADL are presented in Table S2.

Cox regression analyses revealed that, of the EF subdomains, inhibition and processing speed were associated with earlier permanent institutionalization in up to 21 years of follow-up ($P < 0.05$; Table 5). Inhibition remained significant when NIHSS was added in the models.

Discussion

With a comprehensive neuropsychological battery of traditional and less conventional EF tests, different measures for detecting stroke-related EF impairments as well as the associations of specific EF subdomains with post-stroke functional outcome were investigated. The results showed that stroke patients performed significantly more poorly compared to healthy controls in a wide variety of EF tests, including measures of response inhibition, set shifting, initiation, strategy formation and processing speed. The contribution of different EF subdomains on functional impairment varied: in stroke patients, poor inhibition, initiation and slow processing speed were associated with impaired functional outcome as defined by mRS, and poor inhibition with IADL 3 months post-stroke regardless of the severity of neurological stroke symptoms. The ability of set shifting was associated with mRS 15 months after stroke. Furthermore, poor inhibition was significantly associated with the risk for earlier permanent institutionalization despite stroke severity in 21-year follow-up.

Our results support previous findings suggesting that EFs are highly susceptible to stroke-related impairments [23,24]. An extensive battery was used to examine which of the EF tests are able to detect stroke-related deficits in the elderly. All the traditional EF tests as well as the less often used Hayling test and questioning task significantly differentiated stroke patients from the healthy controls. The results indicate that stroke-related executive deficits are clearly detectable even in older patients despite subtle changes in EFs due to aging itself. Of the methods used in this study, the design fluency task was the only test in which the performances did not differ between stroke patients and controls. This task may rely on other cognitive domains besides EFs, such as motor planning [25], affecting both groups similarly due to aging.

Table 4 Executive function subdomains as predictors of functional outcome at 3 and 15 months post-stroke

			Model 1				Model 2			
				95% CI				95% CI		
	Executive function subdomain	*n*	OR	Lower	Upper	*P*	OR	Lower	Upper	*P*
mRS 3 months after stroke mRS > 2	Inhibition	62	0.61	0.45	0.84	0.002	0.53	0.32	0.88	0.014
	Processing speed	62	0.23	0.09	0.58	0.002	0.20	0.06	0.67	0.009
	Set shifting	59	0.74	0.56	0.96	0.024	0.79	0.59	1.07	0.123
	Initiation	62	0.27	0.10	0.71	0.008	0.30	0.10	0.93	0.036
	Strategy formation	61	0.21	0.06	0.74	0.016	0.28	0.07	1.06	0.061
IADL 3 months after stroke IADL < 7	Inhibition	59	0.52	0.33	0.83	0.005	0.51	0.29	0.90	0.020
	Processing speed	59	0.46	0.23	0.89	0.020	0.57	0.26	1.26	0.167
	Set shifting	57	0.79	0.62	1.00.	0.048	0.87	0.69	1.10	0.234
	Initiation	59	0.54	0.28	1.02	0.059	0.65	0.28	1.51	0.317
	Strategy formation	58	0.70	0.34	1.41	0.314	0.94	0.39	2.31	0.897
mRS 15 months after stroke mRS > 2	Inhibition	57	0.89	0.76	1.04	0.133	0.95	0.80	1.13	0.581
	Processing speed	57	0.91	0.71	1.16	0.434	1.06	0.80	1.40	0.699
	Set shifting	54	0.71	0.54	0.94	0.018	0.75	0.56	1.00	0.049
	Initiation	57	0.75	0.38	1.47	0.397	1.09	0.52	2.28	0.815
	Strategy formation	56	0.75	0.35	1.62	0.466	0.95	0.42	2.13	0.891

Logistic regression analyses: model 1 was adjusted for age, sex and education; model 2 was additionally adjusted for NIHSS. CI, confidence interval; IADL, Instrumental Activities of Daily Living; mRS, modified Rankin scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio.

Table 5 Executive function subdomain associations with the risk for permanent institutionalization in 21 years of follow-up

		Model 1				Model 2			
			95% CI				95% CI		
	n	HR	Lower	Upper	*P*	HR	Lower	Upper	*P*
Inhibition	53	0.89	0.82	0.96	0.003	0.89	0.82	0.97	0.005
Processing speed	53	0.86	0.76	0.97	0.016	0.88	0.77	1.01	0.073
Set shifting	50	0.96	0.86	1.09	0.394	0.96	0.86	1.07	0.473
Initiation	53	0.74	0.52	1.05	0.096	0.78	0.55	1.11	0.168
Strategy formation	52	0.39	0.58	1.24	0.847	0.86	0.59	1.25	0.430

Cox regression analyses: model 1 was adjusted for age and education; model 2 was additionally adjusted for NIHSS. CI, confidence interval; HR, hazard ratio; NIHSS, National Institutes of Health Stroke Scale.

According to previous studies, executive dysfunction is related to disability in everyday activities [8,9,26]. In the present study, poor performance in EF tests predicted functional impairment evaluated at 3 and 15 months after stroke. Many of the earlier studies of post-stroke cognitive impairment have evaluated EF as a whole and have not elucidated the importance of the specific EF subcomponents. In this study, poor inhibitory control, evaluated with the Hayling and Stroop tests, and processing speed, evaluated with the Trail Making, Stroop and Hayling tests, were associated with functional impairment 3 months after stroke. Set shifting, evaluated with the Trail Making Test and WCST, predicted functional outcome 15 months after stroke. Moreover, poor inhibitory control was associated with the risk of permanent institutionalization in 21-year follow-up. Deficits in inhibition, set shifting and processing speed have previously been linked with different neurological conditions, such as small vessel disease and mild cognitive impairment, and have also been found to decline to some extent with normal aging [27–31]. Our results suggest that inhibitory control is a stronger determinant for post-stroke functional outcome than the other subdomains of EFs.

The generalizability of the results is limited by a relatively small sample size. The subjects of this subsample had milder stroke symptoms and were younger

compared to the original cohort. Further, missing values in neuropsychological data were associated with stroke severity, suggesting that the patients who fully completed the two neuropsychological assessments may have had milder cognitive impairments than the patients missing a few scores due to more severe stroke. The sample size restricted the use of some statistical methods and therefore factor analysis, for example, could not be used in forming the subdomains of EFs. Although statistical power may have been decreased by sample size, it was possible to show strong associations between EF subdomains and functional impairment. Further advantages of our study are the elaborate assessment of EFs and the longitudinal evaluation of functional abilities including exceptionally far-reaching follow-up of hospitalization data based on national registers.

In conclusion, EFs seem to have a major impact on long-term post-stroke outcome. In the present study, poorer EF test performance was strongly associated with impaired functional abilities. With the use of an extensive battery of EF tests, it was shown that especially poor inhibitory control had prognostic value on the need for permanent institutionalization during long-term follow-up. Our results suggest that a detailed neuropsychological examination of EFs can be useful in predicting the risk of functional disability and institutionalization after stroke.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article:

Table S1. Tests of executive functions.
Table S2. Executive function test performance as predictor of functional outcome.

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